United States
Consumer Product Safety Commission

July 22, 2025

CPSC Staff Statement on: PHOP Class-Based Risk Assessment

The U.S. Consumer Product Safety Commission (CPSC or Commission) contracted with ICF (Contract BPA No. 61320622A0005, Order No. 61320623F2030) to complete a class-based risk assessment of the polyhalogenated organophosphate (PHOP) flame retardant subclass. This statement was prepared by the CPSC staff. ICF produced the accompanying report, "PHOP Class-Based Risk Assessment" (Subtask 3B in the contract), for CPSC staff. The statement and report have not been reviewed or approved by, and may not represent the views of, the Commission.

In the accompanying Subtask 3B report, ICF applied approaches identified in Subtasks 3A (approaches to perform class-based risk assessment analyses) and 4B (guidance document for performing class-base risk assessment) to develop quantitative hazard quotients (HQs)[1] for substances in the PHOP subclass.[2]

ICF first grouped the PHOP chemicals based on two criteria: on levels of quality in exposure data (identified or estimated in an earlier call order Contract BPA No. 61320622A0005, Order No. 61320622F2012) and toxicity reference values (TRVs)[3] (identified, derived, or estimated in Subtask 2B of this contract call order). These separate quality levels were then integrated to arrive at a confidence level in the overall risk assessment. Next, they created probability distributions that represent the likely level of exposure and the likely value of the TRV for individual PHOP flame retardants. Lastly, they produced a cumulative probability estimate combining these two distributions to determine the likelihood of exposure above a level of health concern for each chemical.

The 3B report describes the calculation of HQ values and the levels of quality or confidence of the risk assessments for all PHOP chemicals. Human health risk was evaluated as cumulative probability that exposure to a chemical resulted in a HQ value of greater than 1. ICF found that five chemicals are currently in use with levels of exposure associated with a lower probability of health risk. One chemical was of marginal concern. Sixteen PHOP chemicals had moderate to higher risk of causing health effects, however, most of these also had higher uncertainty due to limited data. Of those 16, four PHOPs raise particular concern because for each the central tendency estimate for exposure is higher than the central tendency estimate of the TRV. Therefore, human exposures to these chemicals are potentially associated with health effects.

[1] HQ is interpreted relative to a value of 1. If HQ≤1, no adverse effects are expected. If HQ>1, then adverse health effects are possible.
[2] The supporting documents cited in the Subtask 3B report from other subtasks of this contract call order as well as deliverables from two earlier call orders (Contract BPA No. 61320622A0005, Order No. 61320622F2011; and Contract BPA No. 61320622A0005, Order No. 61320622F2012) can be found at https://www.cpsc.gov/Business--Manufacturing/Organohalogen-Flame-Retardant-Chemicals-Assessment.
[3] "Toxicity reference value" or TRV quantifies the potency of a substance or estimates the dose level to which people can be exposed for a specified duration of time without experiencing adverse health effects.

MEMORANDUM

To: Eric Hooker, Matthew Cho, and Kristina Hatlelid, CPSC

From: Samantha Snow, Joei Robertson, and Elizabeth Martin, ICF
Mark Bradley and Lynne Haber, University of Cincinnati

Date: January 17, 2025

Re: Task 3B: Apply Class-based Risk Assessment Analyses to Develop Quantitative Risk Estimates for the PHOPs OFR Subclass
(CPSC Contract Number 61320622A0005, CPSC Order Number 61320623F2030)

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1. Introduction

Under CO-9, Subtask 3B seeks to apply class-based risk assessment to develop quantitative hazard quotients (HQs) for the polyhalogenated organophosphate (PHOP) organohalogen flame retardants (OFRs) subclass.

2. Overview of Class-based Risk Assessment

In the Subtask 3A report, we described methods that could be applied to perform class-based risk assessment and potential ways in which these methods may be applied to OFR chemicals in the PHOP subclass.[1]

Based on our findings in the Subtask 3A report, our overall proposal was to assess the PHOP subclass only. CO-1 (Call Order 61320622F2011 under CPSC Blank Purchase Agreement (BPA 61320622A0005)) reclassified some members of the PHOP subclass following the evaluation of the initial list of PHOP subclass members based on chemical factors (e.g., physicochemical properties) and biological factors (e.g., mechanistic data obtained from high-throughput screening and effects observed *in vivo*). In addition, under CO-3 (Call Order No. 61320622F2012 under CPSC Blank Purchase Agreement (BPA 61320622A0005)) exposure data were curated from several databases only for the PHOP subclass.[2] Because this evaluation of chemical and biological factors was not conducted for the polyhalogenated bisphenol aliphatics and functionalized (PHBAF) subclass in CO-1, and no exposure characterization was conducted for the PHBAF subclass in CO-3, we could not perform the same assessment for PHBAFs as for PHOPs.

Our findings from Subtask 3A demonstrate that there are very limited methods by which to perform class-based risk assessment. We focused on a tiered approach based on available data, as proposed in Alexander-White et al. (2022), and addressing uncertainties in data as described by the Environmental Protection Agency (EPA) Office of Pesticides Program (OPP) (EPA, 2002). To

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[1] Reports and supporting documents for CO-9 are available at https://www.cpsc.gov/Business--Manufacturing/Organohalogen-Flame-Retardant-Chemicals-Assessment.
[2] Reports and supporting documents for CO-1 and CO-3 are available at https://www.cpsc.gov/Business--Manufacturing/Organohalogen-Flame-Retardant-Chemicals-Assessment.

this end, we propose performing a probabilistic risk assessment that draws on ideas presented in Silva et al. (2020). In this report we:

- Describe the current availability of data for exposure and toxicity reference values (TRVs)
- Describe the quality of the available data for exposures and TRVs
- Develop uncertainty characterizations for each of these estimates based on the available data (i.e., upper bound, lower bound, shape of distribution)
- Calculate probability distributions to assess the likelihood of exposure and hazard
- Develop cumulative probabilities for HQs greater than 1 based on the quality of the estimates
- Describe information needed to strengthen these estimates.

The chemicals in the PHOP subclass, including CASRNs, chemical names, and (when available) common abbreviations, can be found in Table A-1 of 6.Appendix A.

3. Overview of Availability of Exposure and Toxicity Reference Value Data

This report focuses on noncancer risk assessment based on TRVs derived in the Subtask 2B report and exposure estimates in CO-3. Table 1 describes the availability and quality of exposure and TRV data. Among the 29 confirmed PHOP subclass members, data for both exposure and dose-response existed or were extrapolated based upon available data for 22 chemicals. Specifically, all 29 chemicals had a non-cancer TRV, but 7 of the 29 PHOPs had no exposure data. Because risk assessment relies on the integration of exposure and TRV values, risk assessment could only be performed for 22 chemicals.

The quality of exposure and toxicity data are described in Sections 3.1 and 3.2 respectively. Briefly, exposure data were considered of higher quality when biomonitoring data were available (3 chemicals). Exposure estimates were considered to be of lower quality for all other estimates (19 chemicals), because the exposure estimates were based on limited use-case data, as described in further detail in Section 3.1. The quality of TRV estimates was high for 4 chemicals (formal TRV derivation), medium or low-medium for 7 chemicals (extrapolated data based on empirically determined data), and low or very low for 18 chemicals (an estimate based upon toxicity of other subclass members). One of the chemicals with a low-medium quality TRV did not have any exposure data, and so is listed separately in Table 1. The rationale for the approach to the noncancer TRVs is discussed in Section 3.2.1, and in more detail in the Subtask 2B report. Based on the availability of exposure and TRV data, risk assessment estimates are provided for 22 PHOP chemicals with various degrees of uncertainty based upon data quality (Table 1).

Table 1. Availability and Quality of Data for 29 Confirmed PHOP Subclass Members

CASRN	Abbreviations	Exposure[a]	Noncancer TRV[b]
13674-84-5	TCIPP (Anchor)	Higher	High
115-96-8	TCEP	Higher	High
13674-87-8	TDCIPP	Higher	High

CASRN	Abbreviations	Exposure[a]	Noncancer TRV[b]
38051-10-4	V6; BCMP-BCEP	Lower	High
6294-34-4		Lower	Medium
19186-97-1	TTBNPP	Lower	Medium
140-08-9		Lower	Low-medium
6145-73-9		Lower	Low-medium
115-98-0		Lower	Low-medium
126-72-7	TDBPP	Lower	Low-medium
78-43-3		Lower	Very Low
4351-70-6		Lower	Very Low
5412-25-9	DDBPP	Lower	Very low
6749-73-1		Lower	Very low
66108-37-0		Lower	Very low
33125-86-9		Lower	Very low
76025-08-6		Lower	Very low
1067-98-7		Lower	Very low
76649-15-5		Lower	Very low
5324-12-9	BDBPP	Lower	Very low
27568-90-7		Lower	Very low
84282-27-9		Lower	Very low
1047637-37-5	BCMP-BCMEP	N/A	Medium
98923-48-9		N/A	Very low
53461-82-8		N/A	Very low
61090-89-9		N/A	Very low
72236-72-7		N/A	Very low
26604-51-3		N/A	Very low
34621-99-3		N/A	Very low

CASRN = CAS registry number; TRV = toxicity reference value.
[a] Higher = biomonitoring based on NHANES data; Lower = summed exposure data and Consumer Exposure Model (CEM) estimates available; N/A = no data available.
[b] High = available high-quality TRV; Medium = read across from anchor chemical (relative potency factor [RPF] = 1); Low-medium = apply RPF based on *in vivo* rat median lethal dose (LD_{50}) to anchor chemical; Very low = anchor chemical TRV/10.

3.1. Exposure Data

This report identified three data quality categories for PHOP exposure measures: higher, lower, and no available data (Table 1). For 3 chemicals, higher quality empirical exposure data were available (CO-3 Report, Table 22). These chemicals have urine-based biomonitoring data that were collected in the National Health and Nutrition Examination Survey (NHANES). These data are considered to be higher quality as they directly measure the chemical in a person. While NHANES data provides nationally representative sampling, other population cohorts can also provide useful information for population groups potentially under-sampled in a large-scale national surveillance study. For PHOPs, biomonitoring data sources were considered and were generally consistent with each other and higher-end estimates for non-NHANES individual cohort studies.

For the other 19 chemicals, the available data were considered to be lower quality because <3 data sources existed from <3 empirical exposure data types (biomonitoring, environmental monitoring, epidemiology, ADME, or product testing/source characterization). Thus, to develop an aggregate exposure measure, two approaches were used in CO-3 (Tables 21 and 22). The first was to estimate total exposure by summing up different sources of exposures (e.g., background exposure that are measurements of the OFRs in various environmental media summed with aggregate consumer exposure). This is less certain than a biomonitoring measure as it relies on the experimental accuracy and existence of various environmental measures rather than being a single unified measure of exposure. The second method was to model consumer exposure estimates using the Consumer Exposure Model (CEM) (EPA, 2023). Interestingly, the modeled doses from CEM were higher than high-end NHANES intakes calculated through reverse dosimetry but were sometimes lower than high-end intakes calculated from alternative data sets in the literature (where available for the 3 chemicals), indicating a higher level of uncertainty and the need for future refinement of the CEM input parameters and assumptions used to combine or aggregate scenarios across population groups. Given the differences in the reverse dosimetry doses when compared to the modeled aggregate doses, doses modeled by combination of CEM and aggregate exposure combinations were considered to be lower quality estimates until refined. Once estimates are refined to better match reverse dosimetry estimates, there could be higher confidence in applying these modeled estimates to chemicals that do not have biomonitoring data.

For seven chemicals, there was no available exposure data nor ability to generate estimates based upon available known consumer usage. As such, these chemicals are marked with a "N/A" in Table 1. Since there was no way to estimate exposure to these chemicals, they were not carried forward for risk assessment. This left 22 chemicals for assessment, 3 with higher quality exposure data and 19 with lower quality exposure data.

3.2. Toxicity Reference Value Data

3.2.1. Noncancer Toxicity Reference Values

In the Subtask 2B report, we detailed information regarding TRV derivation. We estimated noncancer TRVs for 29 confirmed members of the PHOP subclass. This was done based on high quality experimental data (for 4 chemicals), limited experimental data (for 7 chemicals), or conservative estimations of dose-response based upon toxicity data for data-rich subclass members (for 18 chemicals). In general, we considered a range of approaches of varying levels of confidence to deriving TRVs. To identify TRVs for as many PHOPs as possible, we applied the highest confidence method available for a given PHOP chemical. When a single chemical had both higher and lower quality data/confidence categories, these data were compared to empirically

inform the choice of TRV and overall level of quality. The specific methods by which we estimated TRVs, additional methods considered, and sensitivity analyses performed can be found in the Subtask 2B report. Here, we report a simplified description that is relevant to the way distributions were derived in Section 4.2.

Of the 29 PHOP chemicals, high quality estimates for the TRVs were obtained for 4 chemicals, as these were derived in the traditional way based on data used in existing assessments (i.e., evaluating study quality and effects, identifying points of departure (PODs) for high-quality studies, and application of uncertainty factors).

For 7 chemicals, limited experimental data existed. For 3 of these chemicals (6294-34-4, 19186-97-1, and 1047637-37-5), there were no agency assessments with TRVs, but PODs were available from the U.S. EPA ToxVal database with limited supporting data. These PODs were substantially higher than those for chemicals with high quality data. This disparity raised substantial uncertainty regarding whether these PODs were sufficiently health protective. Therefore, TRVs were derived for these chemicals based on direct read-across (RAX) from the TRV for the anchor chemical (TCIPP) (equivalent to using a relative potency factor (RPF) of 1). This was considered a health-protective approach by using a related, but lower, TRV that is based on high quality data. The resulting TRVs were considered medium confidence. These 3 chemicals shared critical effects similar to those for the 4 high quality chemicals. These effects were related to reproductive (e.g., effects in testes) and developmental (e.g., increased runts in litters, maternal toxicity) toxicity. Note that for one of these 3 chemicals (BCMP-BCMEP, 1047637-37-5), no exposure estimates were available and so it could not be examined using the full class-based risk assessment. For the remaining 4 chemicals with limited empirical data, TRVs were calculated using RPFs. These chemicals had no repeated dose PODs available, but rat oral median lethal doses (LD_{50}s) were identified for these 4 chemicals as well as 13 additional PHOPs. However, sensitivity analyses in Subtask 2B demonstrated that only the RPFs derived based on rat *in vivo* LD_{50}s <2,000 mg/kg/d were reliable. As such, TRVs were derived using this approach only for these 4 chemicals. The TRVs derived from this approach were considered to be of low-medium quality as no empirical data were available to demonstrate that reproductive or developmental toxicity resulted from exposure to these chemicals.

The remaining 18 chemicals were of low or very low quality in terms of TRV derivation. Within this group of chemicals, 2 had unreliable *in vivo* rat LD_{50}s (LD_{50} >2000 mg/kg/d) and13 had only QSAR data. In general, the QSAR-based LD_{50} values did not correlate well with empirical LD_{50} values, and so the QSAR data were deemed unreliable. The remaining 3 chemicals had no available data. Based on the limitations of the available data or lack of data, the same quantitative method was used to derive the TRVs for the low and very low data quality categories. Specifically, each chemical was assigned a TRV derived by dividing the TRV of TCIPP (the anchor chemical) by 10. Sensitivity analyses showed that this method produced TRV estimates that were consistent with the most sensitive of chemicals with LD_{50}s <2000 mg/kg/d, as well as with TRV estimates derived from a predicted general reproductive/developmental POD (Aurisano et al., 2023; Kvasnicka et al., 2024).

3.2.2. Cancer Toxicity Reference Values

In the Subtask 2B report, we did not derive cancer TRVs. Cancer data were identified for 4 chemicals with existing high-quality assessments: TCEP (115-96-8), TDBPP (126-73-7), TDCIPP (13674-87-8), and TCIPP (13674-84-5). No quantitative assessment is available for TCIPP because the observed uterine tumors had a low weight-of-evidence and the liver tumors appear to be induced by modes of action (MOAs) via the constitutive androstane receptor (CAR), pregnane X receptor (PXR), and peroxisome proliferator-activated receptor alpha (PPARα) signaling pathways

(NTP, 2023) that are not relevant to humans (Felter et al., 2018). The other 3 chemicals all induced kidney tumors in the rat, but TCEP is thought to act via a nongenotoxic MOA, while the other two chemicals (TDBPP and TDCIPP) are thought to act via a genotoxic MOA. While the exact nongenotoxic MOA for TCEP is not entirely known, it may involve a variety of other changes including those related to cell cycle regulation and cell proliferation (U.S. Environmental Protection Agency, 2023). This consistency in target tissue suggested that it might be possible to apply an RPF approach for the other chemicals. However, in sensitivity analyses where existing cancer PODs were compared to estimated cancer PODs derived from RPFs, which in turn were based on either *in vivo* rat LD_{50}s or QSAR-predicted LD_{50}s, estimates varied too substantially to ensure confidence. This mismatch reflects issues with this approach including reliability of the LD_{50} measure as well as potentially reflecting the apparent differences in MOA. Because data-rich members appear to cause cancer via a variety of different mechanisms including a mix of genotoxic and nongenotoxic MOAs (California Environmental Protection Agency, 1992; Faust & August, 2011; National Cancer Institute, 1978; U.S. Environmental Protection Agency, 2023) and in light of the extrapolation issues, class-based cancer TRVs were not derived. Thus, this report will focus only on the noncancer class-based risk assessment.

4. Approaches for Distribution Estimations

4.1. Exposure Data

The chosen distributions parameters for the higher quality and lower quality exposure data for the PHOP chemicals are summarized in Table 2.

Table 2. Distribution Parameters by Exposure Data Quality

Exposure Data Quality	Distribution Type	Central Tendency	Standard Deviation	5th Percentile	95th Percentile
Higher	Log Normal	Reported	Reported	N/A	N/A
Lower	Log Normal	Calculated	Calculated	Summed Environmental Measures	CEM Estimate

N/A = not applicable; CEM = Consumer Exposure Model.

4.1.1. Higher Quality Data

For higher quality exposure data, the geometric mean (GM), standard deviation (GSD), and 95th percentile ($q_{0.95}$) were extracted from NHANES data catalogued in the CO-3 report in Table 22. While NHANES distributions may not capture exposure patterns of specific subpopulations, we used these data to estimate average exposure in the US population. Exposure is characterized with the log normal distribution, where the log-transformed exposure values are normally distributed with population mean (μ) and standard deviation (σ). The GM and GSD data were used to estimate μ and σ using a log transformation (Limpert et al., 2001).

$$\hat{\mu}_{e1} = \log(GM)$$

$$\hat{\sigma}_{e1} = \log(GSD)$$

The $q_{0.95}$ data, $\hat{\mu}_{e1}$, and $\hat{\sigma}_{e1}$ were used to estimate a second set of parameters based on the cumulative distribution function (CDF) for the log normal distribution:

$$P(X < x) = \Phi\left(\frac{\log(x) - \mu}{\sigma}\right) \quad (1)$$

where Φ is the CDF for the standard normal distribution (Johnson et al., 1994). In Equation (1), the value of x corresponding to the desired probability α is the percentile q_α such that:

$$\alpha = \Phi\left(\frac{\log(q_\alpha) - \mu}{\sigma}\right)$$

which can be rearranged as:

$$\Phi^{-1}(\alpha) = \Phi^{-1}\left(\Phi\left(\frac{\log(q_\alpha) - \mu}{\sigma}\right)\right)$$

$$\Phi^{-1}(\alpha) = \frac{\log(q_\alpha) - \mu}{\sigma}$$

$$\log(q_\alpha) = \sigma \times \Phi^{-1}(\alpha) + \mu \quad (2)$$

Equation (2) can be rearranged to solve for μ and σ as:

$$\mu = \log(q_\alpha) - \sigma \times \Phi^{-1}(\alpha) \quad (3)$$

$$\sigma = \frac{\log(q_\alpha) - \mu}{\Phi^{-1}(\alpha)} \quad (4)$$

With equations (3) and (4) second set of parameters was then estimated as:

$$\hat{\mu}_{e2} = \log(q_{0.95}) - \hat{\sigma}_{e1} \times \Phi^{-1}(0.95)$$

$$\hat{\sigma}_{e2} = \frac{\log(q_{0.95}) - \hat{\mu}_{e1}}{\Phi^{-1}(0.95)}$$

The final exposure distribution parameter estimates, $\hat{\mu}_e$ and $\hat{\sigma}_e$, were then calculated as the average of the two estimates.

4.1.2. Lower Quality Data

For lower quality estimates, the 5th percentile ($q_{0.05}$) was defined as the sum of all environmental monitoring data collected in CO-3 and presented in Table 22 of that report. The 95th percentile ($q_{0.95}$) was defined as the values derived from the CEM, which was based on a summing across 18 different consumer product categories and then extrapolating the amount in a human based on rates of migration and absorption. The shape of the distribution was assumed to be log normal based upon empirical evidence that general exposures in the population follow a log normal distribution (Flynn, 2004). These bounds were first used to estimate the log normal parameter σ by plugging the values into Equation (3), setting the estimates equal to each other, and solving for σ:

$$\hat{\mu}_{q05} = \log(q_{0.05}) - \hat{\sigma}_e \times \Phi^{-1}(0.05) = \log(q_{0.95}) - \hat{\sigma}_e \times \Phi^{-1}(0.95) = \hat{\mu}_{q95}$$

$$\hat{\sigma}_e \times \Phi^{-1}(0.95) - \hat{\sigma}_e \times \Phi^{-1}(0.05) = \log(q_{0.95}) - \log(q_{0.05})$$

$$\hat{\sigma}_e = \frac{\log(q_{0.95}) - \log(q_{0.05})}{\Phi^{-1}(0.95) - \Phi^{-1}(0.05)}$$

Similarly, the log normal parameter μ was estimated by plugging values into Equation (4), setting the estimates equal to each other, and solving for μ:

$$\frac{\log(q_{0.95}) - \hat{\mu}_e}{\Phi^{-1}(0.95)} = \frac{\log(q_{0.05}) - \hat{\mu}_e}{\Phi^{-1}(0.05)}$$

$$\Phi^{-1}(0.05) \times (\log(q_{0.95}) - \hat{\mu}_e) = \Phi^{-1}(0.95) \times (\log(q_{0.05}) - \hat{\mu}_e)$$

$$\Phi^{-1}(0.05) \times \log(q_{0.95}) - \Phi^{-1}(0.05) \times \hat{\mu}_e = \Phi^{-1}(0.95) \times \log(q_{0.05}) - \Phi^{-1}(0.95) \times \hat{\mu}_e$$

$$\Phi^{-1}(0.95) \times \hat{\mu}_e - \Phi^{-1}(0.05) \times \hat{\mu}_e = \Phi^{-1}(0.95) \times \log(q_{0.05}) - \Phi^{-1}(0.05) \times \log(q_{0.95})$$

$$\hat{\mu}_e \times \left(\Phi^{-1}(0.95) - \Phi^{-1}(0.05)\right) = \Phi^{-1}(0.95) \times \log(q_{0.05}) - \Phi^{-1}(0.05) \times \log(q_{0.95})$$

$$\hat{\mu}_e = \frac{\Phi^{-1}(0.95) \times \log(q_{0.05}) - \Phi^{-1}(0.05) \times \log(q_{0.95})}{\Phi^{-1}(0.95) - \Phi^{-1}(0.05)}$$

4.2. Toxicity Reference Value Data

The chosen distribution types and rationale for the various TRV data quality categories for the PHOP chemicals are summarized in Table 3; additional information on the rationale for the central tendency and bounds is provided in Table A-2 of 6.Appendix A. A key caveat is that the decisions about distributions described below (i.e., central tendency, bounds, and shape of the distribution) involve significant scientific judgment. The following text describes our rationale for a scientifically-based and health protective distribution for each category of data quality.

Table 3. TRV Distribution Parameters by TRV Data Quality

TRV Quality	Distribution Type	Central Tendency	Standard Deviation	5th Percentile	95th Percentile
High	Normal	TRV	Calculated	TRV/3	TRV*3
Medium	Log Normal	RAX	Calculated	TRV/10	ToxValDB[a] POD/100
Low-Medium	Log Normal	RPF (from empirical rat LD_{50} <2,000 mg/kg/d)	Calculated	TRV/10	Chiu Dashboard[b] POD
Low and Very Low	Log Normal	Anchor chemical/10	Calculated	TTC	100*TRV

TRV = toxicity reference value; RAX = read across; POD = point of departure; RPF = relative potency factor; LD_{50} = median lethal dose; TTC = threshold of toxicological concern.
[a] POD data was identified from the ToxValDB.
[b] PODs were identified from the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024).

4.2.1. High Quality Data

For high quality TRV estimates, it was assumed that the value of the TRV was the mean estimate of the TRV distribution ($\hat{\mu}_{TRV}$) and that the 5th and 95th percentiles of the estimates ($\hat{q}_{0.05}$and $\hat{q}_{0.95}$) were one order of magnitude across both sides of the distribution (i.e., the 5th percentile was equal to the mean divided by 3 and the 95th percentile was equal to the mean multiplied by 3). This distribution is based on the phrase in the definition of the reference dose (RfD) that it is a value with "uncertainty spanning perhaps an order of magnitude." This parenthetical phrase has been interpreted to mean that the RfD is at the upper end, the lower end, or the middle of the range of

an order of magnitude (EPA, 2002) More nuanced considerations recognize that larger uncertainty factors are related to greater uncertainty (Dourson et al., 1996). Because the 4 chemicals with high quality TRV estimates are relatively data rich, we judged that the RfD is in the center of the distribution. A normal distribution shape was chosen to estimate as we assumed that the TRV distribution should be equally sized on either side. Three estimates for the normal distribution standard deviation (σ) were calculated using Equation (4) as:

$$\hat{\sigma}_{TRV1} = \frac{q_{0.05} - \hat{\mu}_{TRV}}{\Phi^{-1}(0.05)}$$

$$\hat{\sigma}_{TRV2} = \frac{q_{0.95} - \hat{\mu}_{TRV}}{\Phi^{-1}(0.95)} \hat{\sigma}_{TRV3} = \frac{q_{0.95} - q_{0.05}}{\Phi^{-1}(0.95) - \Phi^{-1}(0.05)}$$

The average of these three estimates was used as the final estimate $\hat{\sigma}_{TRV}$.

4.2.2. Medium and Low-Medium Quality Data

For medium and low-medium quality TRV estimates, the TRV itself was calculated based on either direct RAX from the anchor chemical (equivalent to an assumed RPF = 1) or an empirically derived RPF, respectively (see Subtask 2B report). The difference between medium and low-medium estimates were related to the value of the RPF. While the chemicals with medium quality TRV estimates could have had TRVs derived directly from empirical PODs identified in ToxValDB using uncertainty factors, confidence in this method was lower and a direct RAX approach was more conservative. On the other hand, RPF estimates for the low-medium quality TRVs were smaller than 1 (thus the chemical was assumed to be more potent than the anchor chemical). The shape of these distributions was estimated to be log normal, to be conservative as the log normal distribution is skewed towards the lower limit of the distribution. For these distributions, the 5th percentile ($q_{0.05}$) was assumed to be the value of the chemical's TRV divided by 10 (TRV/10). A factor of 10 was chosen because some interpret the RfD definition in Section 4.2.1 as meaning an order of magnitude both above and below the RfD instead of the entire range of bounds spanning an order of magnitude. The 95th percentile ($q_{0.95}$) was a chemical specific value, either computationally modeled from the Chiu Dashboard for low-medium chemicals or derived from a POD deposited in ToxValDB (ToxValDB POD/100) for medium chemicals. The ToxValDB POD/100 would have been used as the basis for the TRV if there were higher confidence in those PODs.

These bounds were first used to estimate the parameter σ as described for $\hat{\sigma}_e$ in Section 4.1.2:

$$\hat{\sigma}_{TRV1} = \frac{\log(q_{0.95}) - \log(q_{0.05})}{\Phi^{-1}(0.95) - \Phi^{-1}(0.05)}$$

This value was used to estimate the parameter μ using Equation (4) from Section 4.1.1:

$$\hat{\mu}_{TRV1} = \log(\hat{q}_{0.05}) - \hat{\sigma}_{TRV1} \times \Phi^{-1}(0.05)$$

The sample mean of a log normal distribution for random variable X can be expressed in terms of the parameters μ and σ (Johnson et al., 1994):

$$E(X) = \exp\left(\mu + \frac{\sigma^2}{2}\right) \quad (5)$$

Using Equation (5), a second estimate of μ was calculated by plugging in $\hat{\sigma}_{TRV1}$ and the TRV estimate (E(TRV)) as the log normal sample mean, E(X):

$$E(TRV) = \exp\left(\hat{\mu}_{TRV2} + \frac{\hat{\sigma}^2_{TRV1}}{2}\right)$$

$$\log\big(E(TRV)\big) = \hat{\mu}_{TRV2} + \frac{\hat{\sigma}^2_{TRV1}}{2}$$

$$\hat{\mu}_{TRV2} = \log\big(E(TRV)\big) - \frac{\hat{\sigma}^2_{TRV1}}{2}$$

The final estimate $\hat{\mu}_{TRV}$ was calculated as the average of the two μ estimates.

For chemicals where $\log(E(TRV)) > \hat{\mu}_{TRV1}$, a second estimate of σ was calculated by plugging in $\hat{\mu}_{TRV1}$ and E(TRV) into Equation (5):

$$E(TRV) = \exp\left(\hat{\mu}_{TRV1} + \frac{\hat{\sigma}^2_{TRV2}}{2}\right)$$

$$\log[E(TRV)] = \hat{\mu}_{TRV1} + \frac{\hat{\sigma}^2_{TRV2}}{2}$$

$$\frac{\hat{\sigma}^2_{TRV2}}{2} = \log\big(E(TRV)\big) - \hat{\mu}_{TRV1}$$

$$\hat{\sigma}^2_{TRV2} = 2 \times \left[\log\big(E(TRV)\big) - \hat{\mu}_{TRV1}\right]$$

$$\hat{\sigma}_{TRV2} = \sqrt{2 \times \left[\log\big(E(TRV)\big) - \hat{\mu}_{TRV1}\right]}$$

For the four chemicals with $\hat{\sigma}_{TRV2}$ (TDBPP (126-72-7), 140-08-9, 6145-73-9, and 115-98-0), the average of the two estimates was used as the final estimate $\hat{\sigma}_{TRV}$. Otherwise, $\hat{\sigma}_{TRV1}$ was used as the final estimate.

4.2.3. Low and Very Low Quality Data

For low and very low quality TRV estimates, the TRV is estimated to be the POD for the anchor chemical divided by 10. The 95th percentile was estimated to be the TRV multiplied by 100 (two orders of magnitude) to account for greater uncertainty than for the medium and low-medium categories. The 5th percentile was estimated to be the threshold of toxicological concern (TTC) for Cramer Class III (the most conservative class). For symmetry with the 95th percentile, dividing by a factor of 100 was considered, but the resulting lower bounds were well below the TTC. Given that the TTC itself is supposed to be at or near the lower end of possible TRVs (i.e., designed to be conservative), the TTC was chosen instead. As before, a log normal distribution shape was used as it is more conservative. $\hat{\mu}_{TRV}$ and $\hat{\sigma}_{TRV}$ were calculated as described for medium and low-medium quality data.

4.3. Cumulative Probability Distribution Calculations

Next, we conducted a cumulative probability assessment of the HQ. For this analysis we calculated the HQ according to the following formula:

$$HQ = \frac{Exposure}{TRV}$$

HQ is interpreted relative to a value of 1. If HQ≤1, no adverse effects are expected. If HQ>1, then sensitive populations may begin to experience mild effects. For cases where both exposure and

TRV are assumed to be log normally distributed, the cumulative probability that HQ>1 (CP(HQ > 1)) was calculated from the cumulative distribution function for a log normal distribution with:

$$\mu = \hat{\mu}_e - \hat{\mu}_{TRV} \text{ and } \sigma = \sqrt{\hat{\sigma}_e^2 + \hat{\sigma}_{TRV}^2}.$$

For cases where exposure is assumed to be log normally distributed and TRV is assumed to be normally distributed, 100,000 exposure values were randomly sampled from $LogNormal(\hat{\mu}_e, \hat{\sigma}_e)$ and 100,000 TRV values were randomly sampled from $N(\hat{\mu}_{TRV}, \hat{\sigma}_{TRV})$. The values were divided to generate a simulated sample of 100,000 HQs. CP(HQ>1) was estimated as the proportion of sampled HQ values greater than 1.

In addition to presenting visual representations of each probability distribution, we also present the probability that the HQ is greater than 1. The closer the HQ number is to 1, the larger the concern; the closer the HQ number is to 0, the smaller the concern. A probability of 1 represents the finding that 100% of the time, the HQ is greater than 1, while a probability of 0 represents the finding that 0% of the time, the HQ is greater than 1. In Section 5, we rank the chemicals based on the cumulative probability of overlap to determine chemicals of highest and lowest concern.

5. Hazard Quotient and Probability Distribution Analysis

The first step in this risk assessment process was to integrate the information about data quality used to determine distribution shape for the exposure and TRV for each chemical into a "Risk Assessment Quality" rating for risk for each chemical (Table 4 and in more detail in Table A-3 of Appendix A). Chemicals with higher-quality estimates for both exposure and TRVs were considered to be higher quality risk distribution estimates (highlighted in dark blue in Table 4). Those with a lower quality estimate for exposure and a high, medium, or low-medium estimate for the TRV were considered to be a low-medium quality risk distribution estimate (highlighted in medium blue in Table 4). Those with lower quality exposure estimate and a low or very low quality TRV estimate were considered to be a lower quality risk distribution estimate (highlighted in light blue in Table 4). Exposure levels and TRV levels were then each sampled 100,000 times randomly and divided (according to the equation in Section 4.3) to produce HQs for each chemical. From these simulations, cumulative probabilities were calculated to identify the proportion of the population that was potentially exposed above the TRV.

Table 4. Risk Assessment Quality for PHOP Chemicals

CASRN	Abbreviation	Exposure Quality	TRV Quality	RA Quality
13674-84-5	TCIPP (Anchor)	Higher	High	Higher
115-96-8	TCEP	Higher	High	Higher
13674-87-8	TDCIPP	Higher	High	Higher
38051-10-4	V6; BCMP-BCEP	Lower	High	Low-medium
6294-34-4		Lower	Medium	Low-Medium
19186-97-1	TTBNPP	Lower	Medium	Low-medium
140-08-9		Lower	Low-medium	Low-Medium
6145-73-9		Lower	Low-medium	Low-Medium
115-98-0		Lower	Low-medium	Low-medium
126-72-7	TDBPP	Lower	Low-medium	Low-medium
78-43-3		Lower	Very Low	Lower
4351-70-6		Lower	Very Low	Lower
5412-25-9	DDBPP	Lower	Very low	Lower
6749-73-1		Lower	Very low	Lower
66108-37-0		Lower	Very low	Lower
33125-86-9		Lower	Very low	Lower
76025-08-6		Lower	Very low	Lower
1067-98-7		Lower	Very low	Lower
76649-15-5		Lower	Very low	Lower
5324-12-9	BDBPP	Lower	Very low	Lower
27568-90-7		Lower	Very low	Lower
84282-27-9		Lower	Very low	Lower

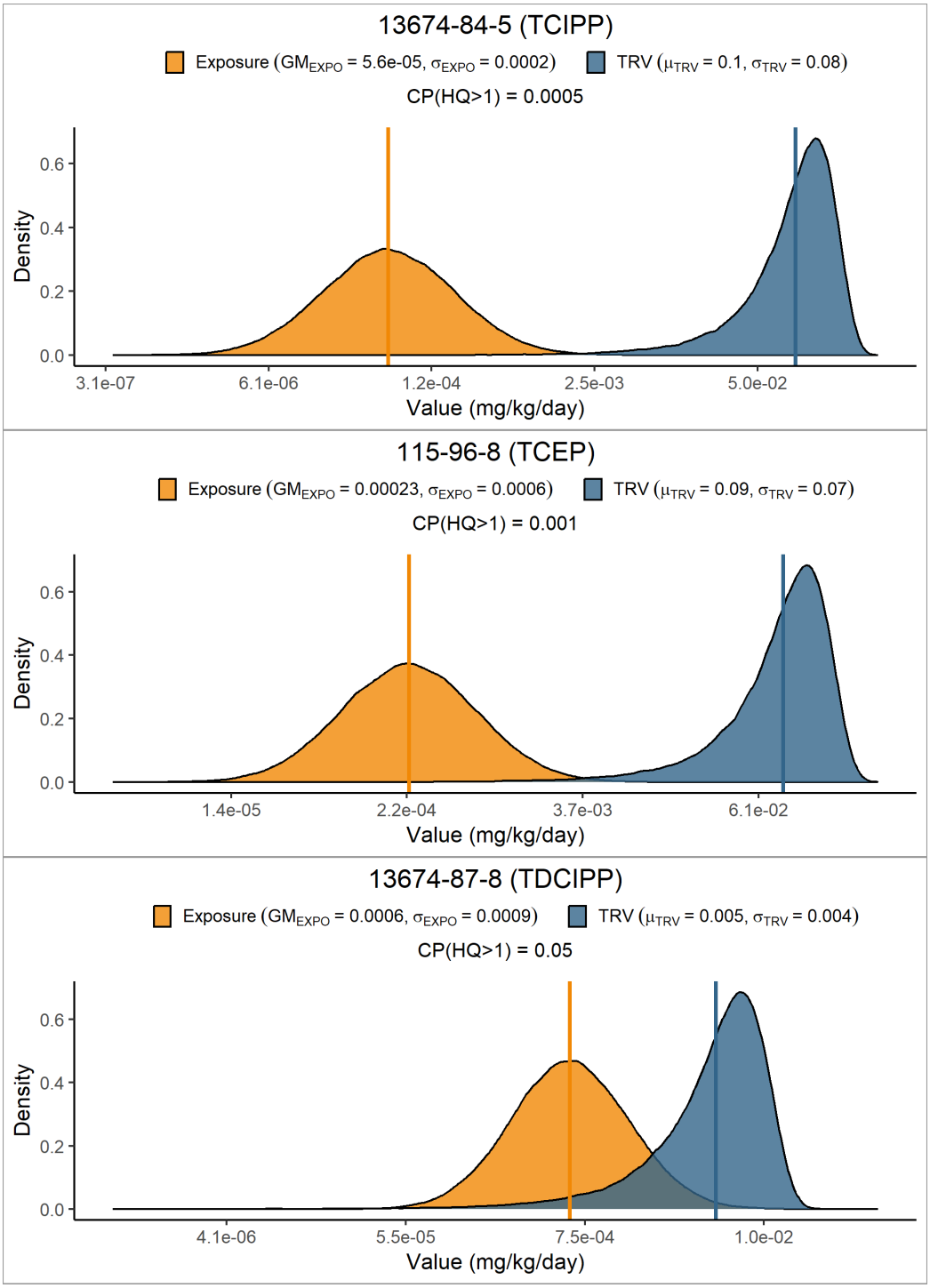
Given that a HQ>1 indicates sensitive populations may begin to experience mild effects, one interpretation of the cumulative probability of HQ>1 is that (at relatively low probabilities) it represents the probability of mild effects developing in sensitive populations based upon the given exposure scenario. Higher probabilities of HQ>1 (and thus presumably higher exceedances) may result in moderate or worse effects in sensitive populations and effects in less sensitive populations. The relationship among the probability of HQ>1, the percentage of the population affected, and severity of effect is not well known, and depends on the chemical-specific shape of the dose-response curve, the effects observed, and the magnitude of the composite uncertainty factor. In light of these considerations, there is not an explicit and straightforward way to interpret the implications of the percent of the population with HQ>1. Based on the approach of Chiu and

Slob (2015), we are considering cumulative probability values below 0.01 (1%, or less than 1 out of 100) to be not of concern, values between 0.01-0.05 (1-5%, or between 1 and 5 out of 100) to be of marginal concern, and values above 0.05 (more than 5%, or more than 5 out of 100) to be of concern (Chiu & Slob, 2015). These levels of concern reflect the definition of the TRV in protecting sensitive populations, and the expectation that small exceedances of the TRV would result in mild effects. Table A-3 summarizes the probability of HQ>1, as well as the central tendency (i.e., a single summary measure that describes the distribution by just the center of the distribution) and standard deviation for the exposure and TRV distributions for each chemical while each section below describes the findings in greater detail.

5.1. Higher Quality Risk Estimates

There were three chemicals with higher quality data available for both TRV and exposure estimates (highlighted in dark blue in Table 4). These were considered to be the chemicals with "higher quality" risk estimates. For the 3 chemicals, TCIPP (1674-84-5), TCEP (115-96-8), and TDCIPP (13674-87-8), higher quality estimates for the TRV and exposure are shown in the figures below. In Figure 1, the estimates for TCIPP and TCEP show very limited overlap between the TRV and exposure; however, for TDCIPP, there is a more significant overlap between the TRV and exposure distributions. This is reflected in the cumulative probabilities of a HQ>1, which shows that TDCIPP has a 0.05 chance of being greater than 1, while TCIPP and TCEP have a 0.0005 and 0.001 chance of being greater than 1, respectively. Overall, the concern for these chemicals was relatively low, particularly for TCIPP and TCEP, with some concern related to exposure to TDCIPP. Note that the x axis uses a log scale. This means that the log normal exposure distribution shows up as normally distributed, while the normal distribution of TRVs looks skewed on the log normal scale

Figure 1. Probability Distribution for Exposure and Toxicity Reference Values and Cumulative Probability of Hazard Quotient Greater than 1 for Higher Quality Toxicity Reference Values and Exposure Data

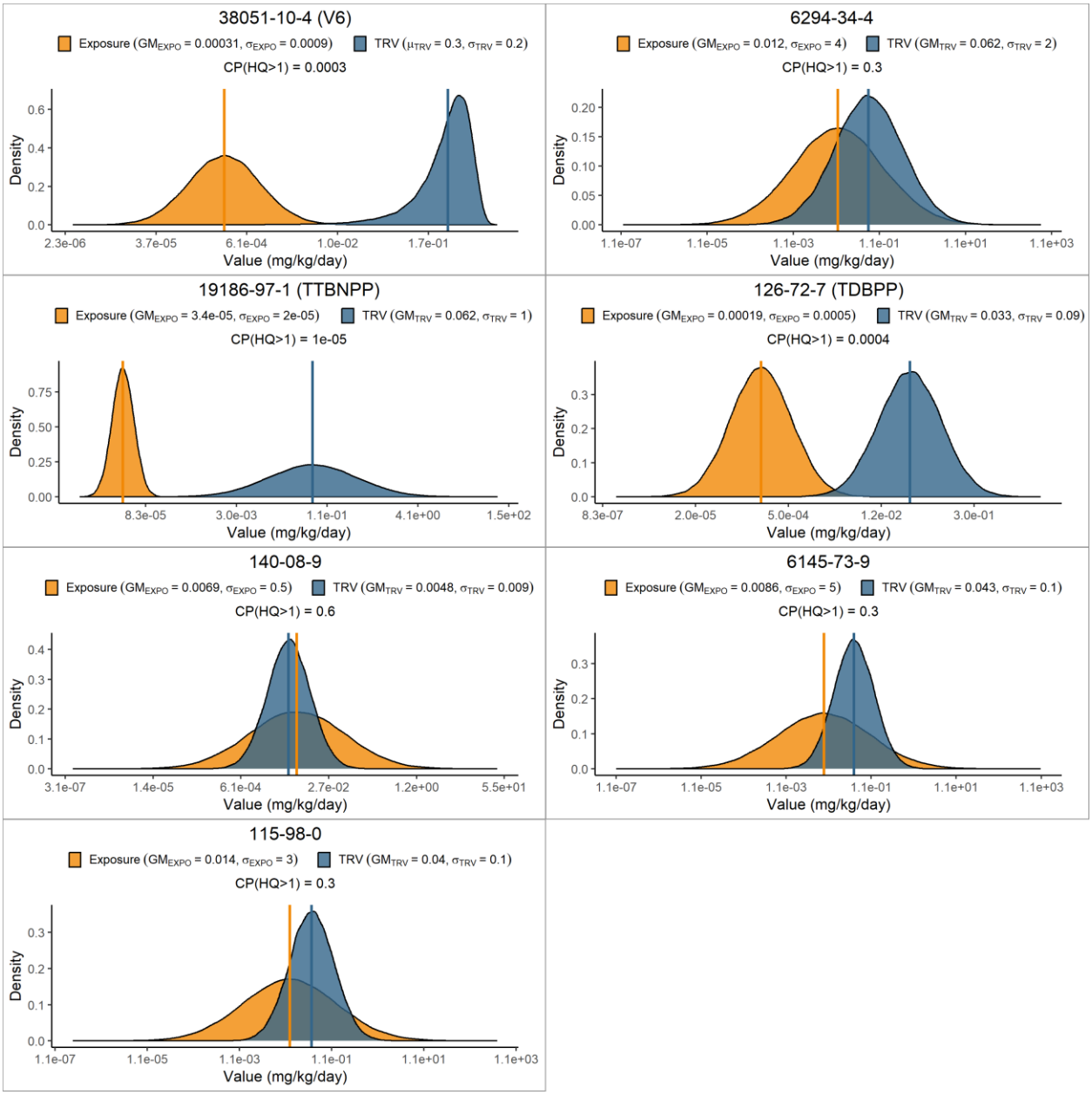


Exposure probability distributions are represented by the orange curves. Toxicity reference value (TRV) probability distributions are represented by the blue curves. Presented on the graph is the cumulative probability (CP) of a hazard quotient (HQ) greater than 1, which represents the overlap of the two distributions. The vertical lines reflect the central tendency for each distribution.

5.2. Low-Medium Quality Risk Estimates

For the low-medium risk quality estimates, there were seven chemicals with high, medium, or low-medium quality data available for the TRV estimate and lower quality data available for the exposure estimates (highlighted in medium blue in Table 4). While the TRV data for all of these chemicals were based upon empirical data (ranging from existing TRVs to those derived based on empirically-based RPFs), they varied in their reliability. The overall risk estimates for all of these chemicals were considered to be "low-medium quality" based on the criteria described at the beginning of Section 5. For 3 chemicals, V6, (38051-10-4), 6294-34-4, and TTBNPP (19186-97-1), high and medium quality estimates were available for the TRV but only lower quality estimates were available for exposure (Table 4 and Table A-3 in Appendix A). Of these chemicals presented in Figure 2, the exposure and TRV distributions for V6 (38051-10-4) and TTBNPP (19186-97-1) were largely non-overlapping. This is reflected in very low cumulative probabilities of a HQ>1, which were 0.0003 and 0.00001, respectively. In contrast, 6294-34-4 had substantial overlap between TRV and exposure distributions (CP=0.3). The other 4 chemicals in this risk assessment quality category had low-medium quality TRV estimates and lower quality estimates for exposure. Of these chemicals, only TDBPP (126-72-7) had largely non-overlapping distributions, which was reflected in the 0.0004 cumulative probability of a HQ>1. The remainder of chemicals had probability distributions that almost entirely overlapped. This is also reflected by high cumulative probabilities of a HQ>1: 140-08-9 (CP=0.6), 6145-73-9 (CP=0.3), and 115-98-0 (CP=0.3). Of these, 140-08-9 is worthy of particular attention since the central tendency estimate of exposure is *above* the central tendency estimate of the TRV, meaning that average exposure in the population is above the likely level at which toxicity-based health outcomes are observed in sensitive subpopulations. For the others with overlapping probability distributions, the central tendency for exposure was within a factor of 10 of the central tendency for the TRV, indicating that the overlap cannot be attributed entirely to wide confidence limits. Of the chemicals within these quality levels, exposures to V6, TTBNPP, and TDBPP are estimated to be below the acceptable risk level.

Figure 2. Probability Distribution for Exposure and Toxicity Reference Values and Cumulative Probability of Hazard Quotient Greater than 1 for Low-Medium Quality Toxicity Reference Values and Exposure Data



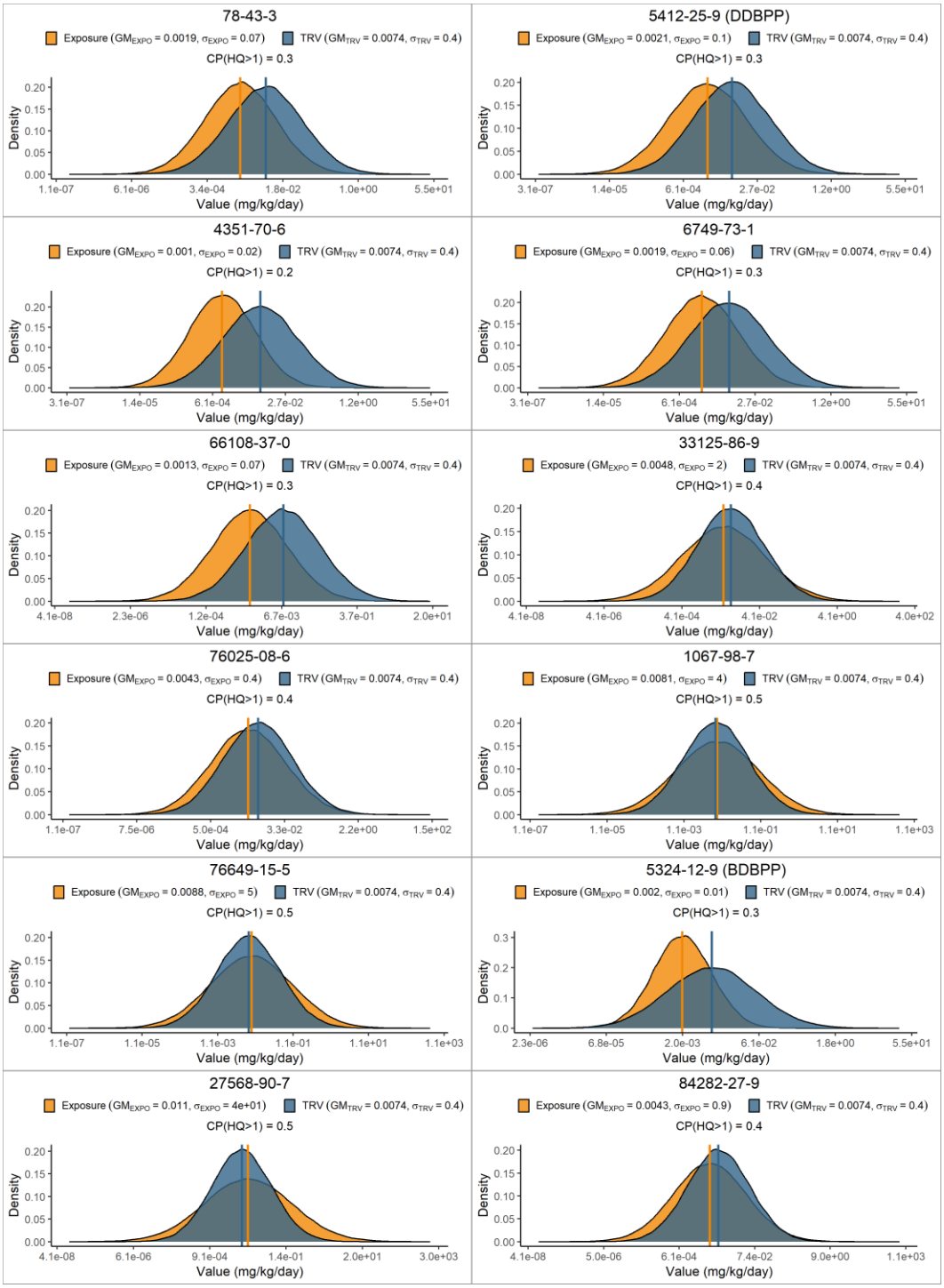
Exposure probability distributions are represented by the orange curves. Toxicity reference value (TRV) probability distributions are represented by the blue curves. Presented on the graph is the cumulative probability (CP) of a hazard quotient (HQ) greater than 1, which represents the overlap of the two distributions. The vertical lines reflect the central tendency for each distribution.

5.3. Lower Quality Risk Estimates

The remaining 12 chemicals (highlighted in light blue in Table 4) were considered to have lower quality risk estimates. The methods used to estimate the TRV were not chemical specific, due to a

general lack of data for these chemicals. Specifically, TRVs for these chemicals were derived by applying general values derived from information about the chemical class as described in Section 4.2.3. As with the low-medium subgroup discussed in Section 5.2, exposure data were of lower quality. For all 12 chemicals, there was substantial overlap between the exposure distribution and the TRV distribution. As such, the cumulative probabilities of a HQ>1 were all very high, ranging from 0.2–0.5. For three of the chemicals in this subgroup (1067-98-7, 76649-15-5, and 27568-90-7), the central tendency for exposure is higher than the central tendency of the TRV, resulting in cumulative probabilities of HQ>1 greater than 0.5. Importantly, it is highly unlikely that these estimates represent the true risk posed to the population as the TRV estimate is highly conservative in an attempt to be health protective. Similarly, the breadth of the exposure distribution is also large, due to uncertainty in CEM estimates. These central tendency values were estimated using conservative, health-protective choices for both exposure (a high-end estimate) and the TRV (a low-end estimate). Because of the lack of data, a conservative estimate of the TRV was used for the risk calculation (i.e., a lower value than might be used for the same chemicals if more data were available for them and thus higher confidence in making an estimate). Because of this conservative approach, there is more limited utility in comparing the central tendency for exposure and for the TRV. In addition, wide confidence intervals were chosen for this group of chemicals, reflecting the high uncertainty about the distribution shape and bounds, which increases the overlap. For the remainder of the chemicals in this group, the central tendency of exposure was less than that for the TRV, but within a factor of about 7, and the probability of an HQ>1 was ≥0.2, indicating that these chemicals were also of concern. Overall, the major conclusion is that more information is needed to better estimate risk for this group of chemicals.

Figure 3. Probability Distribution for Exposure and Toxicity Reference Values and Cumulative Probability of Hazard Quotient Greater than 1 for Lower Quality Toxicity Reference Values and Exposure Data



Exposure probability distributions are represented by the orange curves. Toxicity reference value (TRV) probability distributions are represented by the blue curves. Presented on the graph is the cumulative probability (CP) of a hazard quotient (HQ) greater than 1, which represents the overlap of the two distributions. The vertical lines reflect the central tendency for each distribution.

6. Discussion

In this report we set out to perform class-based risk assessment for PHOP flame retardants. Generally, we did this by first grouping chemicals based on the available data. Initial groupings were based separately on levels of quality in exposure data (identified or estimated in CO-3) and TRVs (identified, derived, or estimated in CO-9 Task 1 or Subtask 2B). These separate quality levels were then integrated to arrive at a confidence level in the overall risk assessment. Next, we created probability distributions that represent the likely level of exposure and the likely value of the TRV for individual PHOP flame retardants. Lastly, we performed a cumulative probability estimate combining these two distributions to determine the likelihood of exposure above a level of health concern for each chemical.

When considering the general findings around risk estimates, we found a relationship between decreasing data availability and increasing cumulative probability of a HQ of concern. This is likely related to both the conservative approaches used for estimating central tendencies of exposure and TRVs when data were limited, and the increased breadth of the exposure and TRV distribution with decreasing (amount and/or quality of) available data. Specifically, to compensate for increased uncertainty in the estimate of the level of exposure as well as health effect, the confidence interval around the central estimate was widened. This led to a higher probability of an overlap between the exposure and TRV distributions.

Of the cumulative probabilities we calculated for subclass members, we found that 5 chemicals, TCIPP (1674-84-5), TCEP (115-96-8), V6 (38051-10-4), TTBNPP (19186-97-1), and TDBPP (126-72-7) are currently in use at an acceptable level (all CP(HQ>1) ≤ 0.01). One chemical, TDCIPP (13674-87-8), is of marginal concern (CP(HQ>1) = 0.05). The remaining 16 chemicals had cumulative probabilities ≥0.2 and as high as 0.6 of HQ>1. Four of these are worthy of particular attention, 140-08-9, 1067-98-7, 76649-15-5, and 27568-90-7, because the central tendency for exposure is higher than the central tendency of the TRV. Importantly, for these four chemicals, the overlap between exposure and the TRV cannot be explained by the wide distributions. Rather it is necessary to determine whether the overlap is real, or whether it results from over-conservative estimates of exposure and the TRV. If the overlap is real, this could indicate that these chemicals are present at levels of exposure that are likely associated with health effects above the level of acceptable risk.

One important caveat of the approach developed here, particularly for lower quality risk estimates, is that these probabilities of HQ>1 are likely overinflated due to the relatively broad estimate of the confidence intervals associated with our estimation method, and the health-protective approach used to estimate the central tendency TRVs, which would also drive down the TRV and increase the probability of HQ>1. Among the chemicals having higher-quality data, only TDCIPP has significant real-world data suggesting a need for reduction in use. For low-medium chemicals such as V6, TTBNPP, and TDBPP, existing data on exposure and health effects were able to substantially improve the estimates of risk. As such, the very high estimates observed for data poor subclass members indicate the need for better assessment of exposure and the TRV.

Overall, the above method of determining class-based risk estimates is unique in that it makes maximal use of the available data, taking into account the uncertainties associated with each data stream. For example, as data are collected under CO-6, better estimates of exposure can be made for a large number of chemicals, which will improve the certainty in the HQ. Additionally, the methodology is flexible. As demonstrated by the approach taken for hazard, bounding of the distribution can be changed based upon available data sources. Where available, the highest quality estimates are used to estimate both the central tendencies and the bounds of the

distribution. This approach could also be applied to exposure as more data becomes available. Specifically, choices about where the 5th, 95th, and central tendencies of a distribution can be recharacterized as data becomes more available from CO-6. Similarly, if additional hazard data becomes available, the distribution around the TRV can be similarly recharacterized. This flexibility is of great value when considering the speed at which new data may be generated or collated.

Taken together, our findings demonstrate an approach to conducting class-based risk assessment. The confidence in and usefulness of the risk estimates are dependent upon the quantity and quality of the data available for each subclass member. Further we show that even limited increases in data, related both to the TRV and exposure, result in better risk estimates. These findings suggest that undertaking studies that increase information about both toxicity thresholds and exposure estimates is of great utility.

Appendix A.

Table A-1. PHOP Chemicals

CASRN	Chemical Name	Common Acronym
5324-12-9	2,3-Dibromopropylphosphate	BDBPP
1047637-37-5	2,2-Bis(chloromethyl)-1,3-propanediyl tetrakis(1-chloro-2-propanyl) bis(phosphate)	BCMP-BCMEP
1067-98-7	Tris(3-chloropropyl)phosphate	N/A
115-96-8	Tris(2-chloroethyl) phosphate	TCEP
115-98-0	Bis(2-chloroethyl) vinylphosphonate	N/A
126-72-7	Tris(2,3-dibromopropyl) phosphate	TDBPP
13674-84-5	Tris(2-chloroisopropyl)phosphate	TCIPP
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate	TDCIPP
140-08-9	Tris(2-chloroethyl) phosphite	N/A
19186-97-1	Tris(tribromoneopentyl)phosphate	TTBNPP
26604-51-3	Tris(dichloropropyl) phosphate	N/A
27568-90-7	Ethanol, 2-bromo-, phosphate (3:1)	N/A
33125-86-9	Phosphoric acid, 1,2-ethanediyl tetrakis(2-chloroethyl) ester	N/A
34621-99-3	Tetrakis(1-chloropropan-2-yl) ethane-1,2-diyl bis(phosphate)	N/A
38051-10-4	Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester	V6; BCMP-BCEP
4351-70-6	Phosphonic acid, P-[1-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, 1-[bis(2-chloroethoxy)phosphinyl]ethyl 2-chloroethyl ester	N/A
53461-82-8	Diethylene glycol bis[bis(2-chloroethyl)phosphate]	N/A
5412-25-9	Bis(2,3-dibromopropyl) hydrogen phosphate	DDBPP
61090-89-9	2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-, 3,9-dioxide	N/A
6145-73-9	Tris(2-chloropropyl) phosphate	N/A
6294-34-4	Bis(2-chloroethyl) 2-chloroethylphosphonate	N/A
66108-37-0	2,2-Bis(bromomethyl)-3-chloropropyl bis[2-chloro-1-(chloromethyl)ethyl] phosphate	N/A
6749-73-1	Tris(1,3-dichloropropan-2-yl) phosphite	N/A
72236-72-7	Bis(1,3-dichloropropan-2-yl) hydrogen phosphate	N/A
76025-08-6	Bis(2-chloro-1-methylethyl) 2-chloropropyl phosphate	N/A
76649-15-5	(2-Chloro-1-methylethyl) bis(2-chloropropyl) phosphate	N/A
78-43-3	Tris(2,3-dichloropropyl)phosphate	N/A
84282-27-9	2-Bromoethyl 5-bromopentyl 2-chloroethyl phosphate	N/A
98923-48-9	4-Bromo-2-chlorobutyl 3-bromo-2,2-dimethylpropyl phosphate	N/A

N/A = not applicable.
Five chemicals were removed from the PHOP subclass under CO-1 (2788-11-6, 1373346-90-7, 49690-63-3, 7046-64-2, 35656-01)

Table A-2. PHOP Chemicals Toxicity Reference Value Derivation and Bounding Approach by Confidence Category

Confidence	TRV Derivation Basis and Approach	Upper Bound		Lower Bound	
		Formula or Source	Basis	Formula or Source	Basis
High	High quality TRV based on published assessment	TRV*3	RfD definition – uncertainty spanning perhaps an order of magnitude centered on the RfD	TRV/3	RfD definition – uncertainty spanning perhaps an order of magnitude centered on the RfD
Medium	Have ToxValDB[a] numbers that are less conservative; Read across from anchor chemical using an RPF = 1 would be more conservative.	POD from the ToxValDB study/100	Considering ToxValDB POD as high end reasonable POD	TRV/10	Some interpret RfD definition as order of magnitude below the RfD
Low-medium	No TRV, empirical rat LD_{50} <2,000; RPF based on *in vivo* rat LD_{50}	Chemical-specific value	Based on Chiu Dashboard[b]	TRV/10	Some interpret RfD definition as order of magnitude below the RfD; One chemical is slightly below the TTC, but this is plausible, given that the TTC is based on a percentile of the distribution
Low	No TRV, empirical rat LD_{50} >2,000; TRV = anchor chemical TRV/10	100x TRV	Larger uncertainty than the low-medium confidence category	TRV/100 considered for symmetry, but this was lower than the TTC for all chemicals so defaulted up to the TTC	Larger uncertainty than the low-medium confidence category
Very low	QSAR-based RPF or no QSAR data; anchor chemical TRV/10	100x TRV	Larger uncertainty than the low-medium confidence category	TRV/100 considered for symmetry, but this was lower than the TTC for all chemicals so defaulted up to the TTC	Larger uncertainty than the low-medium confidence category

TRV = toxicity reference value; RfD = reference dose; POD = point of departure; LD_{50} = median lethal dose; RPF = relative potency factor; TTC = threshold of toxicological concern; QSAR = quantitative structure-activity relationship.

[a] POD data was identified from the ToxValDB.

[b] PODs were identified from the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024).

Table A-3. Risk Assessment Quality with Central Tendencies for PHOP Chemicals

CASRN	Exposure Quality [a]	TRV Quality	Risk Assessment Quality	Abbreviation	CP(HQ>1)	TRV Central Tendency (mg/kg/d)	TRV SD (mg/kg/d)	Exposure Central Tendency (mg/kg/d)	Exposure SD (mg/kg/d)
13674-84-5	Higher	High	Higher	TCIPP (Anchor)	0.0005	0.1	0.08	6E-05	0.0002
115-96-8	Higher	High	Higher	TCEP	0.001	0.09	0.07	0.0002	0.0007
13674-87-8	Higher	High	Higher	TDCIPP	0.05	0.005	0.004	0.0006	0.001
38051-10-4	Lower	High	Low-medium	V6; BCMP-BCEP	0.0003	0.3	0.2	0.0003	0.001
6294-34-4	Lower	Medium	Low-medium		0.3	0.062	0.7	0.012	0.8
19186-97-1	Lower	Medium	Low-medium	TTBNPP	1.0E-05	0.062	0.6	3E-05	5E-05
140-08-9	Lower	Low-medium	Low-medium		0.6	0.0048	0.009	0.0069	0.2
6145-73-9	Lower	Low-medium	Low-medium		0.3	0.043	0.1	0.0086	0.7
115-98-0	Lower	Low-medium	Low-medium		0.3	0.04	0.1	0.014	0.7
126-72-7	Lower	Low-medium	Low-medium	TDBPP	0.0004	0.033	0.08	0.0002	0.0006
78-43-3	Lower	Very Low	Lower		0.3	0.0074	0.1	0.0019	0.03
4351-70-6	Lower	Very Low	Lower		0.2	0.0074	0.1	0.001	0.01
5412-25-9	Lower	Very low	Lower	DDBPP	0.3	0.0074	0.1	0.0021	0.04
6749-73-1	Lower	Very low	Lower		0.3	0.0074	0.1	0.0019	0.03
66108-37-0	Lower	Very low	Lower		0.3	0.0074	0.1	0.0013	0.02
33125-86-9	Lower	Very low	Lower		0.4	0.0074	0.1	0.0048	0.4
76025-08-6	Lower	Very low	Lower		0.4	0.0074	0.1	0.0043	0.1
1067-98-7	Lower	Very low	Lower		0.5	0.0074	0.1	0.0081	0.6
76649-15-5	Lower	Very low	Lower		0.5	0.0074	0.1	0.0088	0.7
5324-12-9	Lower	Very low	Lower	BDBPP	0.3	0.0074	0.1	0.002	0.009
27568-90-7	Lower	Very low	Lower		0.5	0.0074	0.1	0.011	3
84282-27-9	Lower	Very low	Lower		0.4	0.0074	0.1	0.0043	0.2

TRV = toxicity reference value; SD = standard deviation.

[a] Seven PHOP subclass members were not included in the full class-based risk assessment because they did not have any exposure estimates available. These include one chemical with a medium-quality TRV estimate (1047637-37-5 (BCMP-BCMEP)), and six chemicals with very low quality TRV estimates (98923-48-9, 53461-82-8, 61090-89-9, 72236-72-7, 26604-51-3, 34621-99-3).

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